



## CASE REPORT

# Haemophagocytic lymphohistiocytosis following culture-proven pneumococcal infective endocarditis of the tricuspid valve

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We report a case of a 2-year-old boy presenting with persistent fever and splenomegaly who fulfilled the diagnostic criteria for haemophagocytic lymphohistiocytosis (HLH) according to the Histiocyte Society (2004). The persistence of a cardiac murmur despite multiple transfusions, and therapy which rendered him afebrile, led us to do an echocardiogram as part of surveillance for sepsis. This revealed tricuspid vegetation and a small ventricular septal defect. Blood culture and postoperative histology of the anterior leaflet of the tricuspid valve confirmed *Streptococcus pneumoniae* infection. The patient was successfully treated with intravenous antibiotic therapy for 6 weeks and dexamethasone for 8 weeks and remains well and in remission (from HLH) a year later with residual tricuspid regurgitation awaiting tricuspid valve replacement.

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Haemophagocytic lymphohistiocytosis (HLH) is a reactive disorder resulting in generalised proliferation of histiocytes which phagocytose erythrocytes, platelets, leukocytes and their precursors. In addition, high levels of cytokines are produced which result in excessive activation of monocytes. The condition is also characterised by impaired natural killer cell function.<sup>1</sup>

Primary HLH is a familial disorder with an autosomal recessive inheritance pattern. Dysregulation of the natural killer cell and T cell functioning of the immune system are responsible for the clinical syndrome seen in HLH. Currently 5 genetic loci are identified, each resulting in a different subtype of the disease. The gene product of each of these genes is involved in cytotoxic natural killer and T cell function of the immune system.<sup>2</sup> Secondary HLH is an acquired disorder due activation of the immune system by an infection, malignancy and rarely collagen vascular disease.<sup>1</sup>

There is a wide repertoire of microbials which can precipitate HLH. This primarily includes viral agents: Epstein-Barr virus, human herpes virus 6, cytomegalovirus, adenovirus, parvovirus B19, varicella, measles, hepatitis, herpes simplex virus and human immunodeficiency have all been described.<sup>3</sup> In addition, several bacterial (*Salmonella typhi*, mycobacterium, rickettsia, brucellosis and mycoplasma infections), protozoal, parasitic (malaria and leishmaniasis) and rarely fungal organisms (histoplasmosis) have been implicated.<sup>3</sup>

Diagnosis of this condition is based on a combination of clinical and laboratory findings as described in HLH Guidelines: HLH-2004.<sup>4</sup> Based on these guidelines a diagnosis of HLH can be made if one or both of the following criteria are present: (i) a molecular diagnosis consistent with HLH; or (ii) five of the eight diagnostic criteria for HLH.<sup>5</sup>

The eight HLH diagnostic criteria include fever, splenomegaly, cytopenias (affecting two of three lineages in the peripheral

blood: haemoglobin <9 g/dl in patients ≥4 weeks old and <10 g/dl in patients <4 weeks, platelets <100 × 10<sup>9</sup>/l, neutrophils <1.0 × 10<sup>9</sup>/l), hypertriglyceridaemia (fasting triglycerides >3.0 mmol/l) or hypofibrinogenaemia (fibrinogen <1.5 g/l), haemophagocytosis in bone marrow, spleen or lymph nodes with no evidence of malignancy, low or absent NK cell activity (according to local laboratory reference), elevated ferritin (ferritin >500 mg/l) and soluble CD25 (i.e. soluble interleukin-2 receptor) above the normal limit for age.<sup>4,5</sup>

We report a case of a 26-month-old boy with HLH secondary to pneumococcal infective endocarditis of his tricuspid valve which to our knowledge has not been previously described.

## Case report

A 2-year-old boy was referred to a tertiary referral centre with a 3-week history of fever, anorexia, loss of weight and associated intermittent vomiting and diarrhoea. He had no history of coughing, bone pain, bruising or bleeding.

He was fully immunised, although it is noteworthy that prior to his presentation conjugate pneumococcal vaccine was not yet included in the South African national immunisation schedule.

On examination he was pyrexial (39.5°C), underweight for age and stunted. He was markedly pale and noted to have peri-orbital oedema. He had no skin rashes or significant lymphadenopathy. He was tachycardic (140 beats/min) with a grade 3/6 pansystolic murmur audible at the lower left sternal border, a palpable 6 cm, firm hepatomegaly and a firm 3 cm splenomegaly. Urine dipstick did not show microscopic haematuria and there were no other stigmata of sub-acute bacterial endocarditis.

His full blood count showed a bicytopenia and severe microcytic anaemia (Hb 4.5 g/dl and MCV 59.6 fl; platelets 31 × 10<sup>9</sup>/l). His

white blood count was normal ( $18.8 \times 10^9/l$ ). The differential count showed a marked left shift with toxic granulation and no blasts. His corrected reticulocyte count was inappropriately low for his haemoglobin (1.39%). HIV ELISA was non-reactive. Serum C-reactive protein was elevated at 180 mg/l. Iron studies were done to confirm the diagnosis of iron deficiency. The serum ferritin was markedly raised (6 502 µg/l). Coagulation studies revealed a low serum fibrinogen (1.0 g/l) with a normal INR and PTT. His serum triglycerides were markedly elevated at 4.6 (1.1 – 1.9 mmol/l). His initial LDH was 643 mmol/l (ALT 39 U/l) and he had an ESR of 25 mm/hr.

Epstein-Barr virus IgM was negative. Epstein-Barr viral load was 1 607 copies/ml, log value 3.21 (within acceptable limits for our population). A chest X-ray showed an increased cardiothoracic index. There was no significant hilar adenopathy and the lung fields were clear. An abdominal ultrasound confirmed a radiologically enlarged spleen with no focal lesions, adenopathy or ascites. A bone marrow aspirate and trephine revealed a marked infiltration of CD 68 positive histiocytes with evidence of haemophagocytosis. A lumbar puncture was not done because there was no suspicion of central nervous system involvement.

Initially he was commenced on intravenous ceftriaxone 50 mg/kg daily and transfused with blood and platelets. After 5 days he was changed to piperacillin tazobactam and amikacin when the temperature did not settle. He fulfilled seven of the eight criteria for diagnosis of HLH: documented fever, splenomegaly, severe bicytopenia, hyperferritinaemia, hypofibrinogenaemia and hypertriglyceridaemia and haemophagocytosis on bone marrow biopsy with no evidence of leukaemia. Assays for soluble CD 25 and NK cell activity are not available at our institution.

Intravenous dexamethasone at 10 mg/m<sup>2</sup> was commenced. It is our practice to reserve intravenous etoposide and oral cyclosporine for proven EBV-driven HLH.

The diagnosis of HLH was made 8 days after presentation. There was a dramatic clinical response to dexamethasone. His subsequent



**Right-sided infective endocarditis is not common in children with structurally normal hearts and who do not have indwelling central venous lines.**

markers are shown in Table 1. Antibiotic therapy was stopped after his temperature settled and cultures remained negative.

The cardiac murmur that had been noted on admission was initially thought to be secondary to a hyperdynamic circulation due to his marked anaemia and pyrexia. It persisted despite transfusions and dexamethasone. This prompted us to do an echocardiogram which revealed a 6 mm peri-membranous ventricular septal defect (VSD) and large 16 x 22 mm vegetation on the tricuspid valve. He was recommenced on triple antibiotic therapy with intravenous penicillin G, cloxacillin and gentamicin. Prior to administration of these antibiotics his blood grew *Streptococcus pneumoniae* which was sensitive to penicillin. After commencement of triple antibiotics, a Portocath was inserted because of poor venous access. Two days later the vegetation was surgically removed and an anterior valvuloplasty was performed under cardiac bypass. Histopathology confirmed

gram-positive cocci focally in chains within the vegetation.

Postoperatively he developed a pericardial effusion which resolved with diuretic therapy and did not necessitate pericardiocentesis. Triple antibiotic therapy was continued for 2 weeks, after which gentamicin was stopped. Penicillin G and cloxacillin were continued for a total of 26 days. Subsequently, the Portocath became infected with culture-proven *Klebsiella pneumoniae* sensitive to meropenem. He received appropriate intravenous therapy for 10 days after immediate removal of the device.

Dexamethasone was continued throughout for a total of 8 weeks. The dose was halved every 2 weeks, tapered and then stopped. He has now been followed up by both the Cardiology and Haematology/Oncology teams for 18 months, since stopping dexamethasone. Ferritin, fibrinogen and triglyceride levels have remained normal, as have his blood count (Table 1). Follow-up echocardiograms show marked residual tricuspid regurgitation and a small restrictive VSD for which he receives maintenance oral diuretic therapy. He continues to grow well and remains in the care of the cardiology services. A tricuspid valve replacement is planned for the future.

**Table 1. Blood investigations over the course of treatment**

Date	WBC	Haemoglobin	Platelets	Fibrinogen	Triglycerides	Ferritin
At diagnosis	19.6	4.5	45	1.0		1 502
Week 1	26.4	10.4	72		4.6	
Week 2	53.3	10.7	213	0.8	2.9	964
Week 3	14.8	10.9	356	4.4	1.7	245
Week 5	8.6	12.8	463	2.2	1.8	139
Week 6	16	13.4	Clumped	3.1	1.9	213
Week 16	10.6	11.9	283	4.1	1.0	125
Week 20	12.6	12.9	482	3.8	2.7	151
Week 25	9.5	12.4	400	3.3	1.4	97
Week 46	9.3	12.4	340			
Week 58	8.7	13.7	274			
Week 79	9.5	12.2	309			
Week 83	8.7	12.2	406			

## Discussion

*Streptococcus pneumoniae* is a common pathogen in paediatrics, known to be the primary cause of many respiratory tract infections. Despite this, we could not find any reports of the organism being implicated as a causative infection for triggering secondary HLH.

This young patient was an immuno-competent child. *Streptococcus pneumoniae* was cultured on his initial blood culture and confirmed with the histological finding of gram-positive cocci in chains in the vegetation removed from his tricuspid valve. From this we concluded it must have been the infection that precipitated his HLH.

Right-sided infective endocarditis is not common in children with structurally normal hearts and those who do not have indwelling central venous lines. For this reason we would not have initially expected this condition in our patient. The finding of a previously undiagnosed small, peri-membranous VSD on echocardiogram in this patient, however, offers an explanation as to why his tricuspid valve was involved. Alterations to intracardiac blood flow caused by VSDs are known to make these patients more susceptible to infective endocarditis involving the tricuspid valve.<sup>6</sup> Streptococci and staphylococci remain the most common causative organisms.

Current management guidelines for the treatment of HLH recommend the use of a combination dexamethasone, etoposide and cyclosporine (HLH 2004) as first-line therapy. Fully cognisant of the fact that single-agent therapy for HLH is not ideal or recommended,<sup>3</sup> the socio-economic environment of many of our patients, the high incidence of tuberculosis and HIV infection, and the high cost of

cyclosporin justified an informed institutional policy decision to treat only proven EBV-driven HLH with cyclosporine and etoposide upfront along with dexamethasone. Outside of this we reserve the use of the former two agents for refractory or relapsed disease. All other patients with secondary HLH get dexamethasone alone. We have had sufficient success with this strategy to believe that it has a role to play in our setting.

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